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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,403	08/12/1999	WILLIAM R. ARATHOON		2534

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/373,403	ARATHOON ET AL.	
	Examiner	Art Unit	
	ANNE L. HOLLERAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 7/21/2008 is acknowledged.

Claims 56-77 are pending and examined on the merits.

Claim Rejections Withdrawn:

Claim Rejections - 35 USC § 112

The rejection of claim 77 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants' persuasive arguments.

The rejection of claims 56, 58-68, 70, 71 and 73-76 under 35 U.S.C. 103(a) as being obvious over Carter-A (US 5,731,168 issued Mar. 24, 1998; effective filing date is March 1, 1995; cited in a previous Office action 11/02) in view of de Kruif-A (de Kruif, J. et al. The Journal of Biological Chemistry, 271 (13): 7630-7634, 1996; cited in IDS) and further in view of de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS) is withdrawn in view of applicants' statements that the Carter-A and the instant application were, at the time the invention of the instant application was made owned by Genentech, Inc; and that therefore Carter-A cannot preclude patentability of the presently claimed invention under 35 USC 103.

Claim Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-72 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record with respect to claim 67.

Claim 67 is indefinite because section (i) appears to contradict the description of the polypeptides set forth in subsection (b). Section (i) is a selecting step where at least three nucleic acids are selected, a nucleic acid encoding a first polypeptide, a nucleic acid encoding a light chain and at least one additional nucleic acid encoding at least one additional polypeptide, whereas, subsection (b) describes a first polypeptide and an at least one additional polypeptide as each comprising a binding domain that comprises a heavy chain variable domain and a light chain variable domain. Thus, there does not need to be a nucleic acid encoding a light chain, if the nucleic acid encoding a first polypeptide that comprises a light chain variable domain.

Applicants argue that the examiner has misinterpreted subsection (b) of claim 67; and that the present specification provides that "binding sites of the multivalent antibody herein are each preferably formed by a heavy and light chain variable domain"; and that the binding site recited in subsection (b) comprises a light chain variable domain from the light chain polypeptide expressed in (iii) and a heavy chain variable domain.

This is not found persuasive because section (i) directs one to select three separate nucleic acids, where one nucleic acid encodes a light chain, which implies that one polypeptide

chain is a light chain and that the type of antibody made by the method is one where the heavy and light chains are associated together but not tethered together by a linker region (e.g. as in an scFv). However, the problem in subsection (b) is that the "first polypeptide" and "each additional polypeptide" each comprise both heavy and light chain variable domains (e.g. as in an scFv). Therefore, while step (i) appears to be directed to a method of making an antibody with separate light chain, subsection (b) appears to be describing the formation of scFv, where the light chain variable domain and the heavy chain variable domain are linked together by a linker region as in an scFv-type antibody.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56, 58-68, 70, 71 and 73-76 remain rejected under 35 U.S.C. 103(a) as being obvious over Carter-B (WO 96/27011; published 6 Sep., 1996; cited in IDS) in view of de Kruif-A (de Kruif, J. et al. The Journal of Biological Chemistry, 271 (13): 7630-7634, 1996; cited in IDS) and further in view of de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS) for the reasons of record.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that the examiner has not established a prima facie case of obviousness based on an "obvious to try" rationale, and that the references do not teach or suggest all of the elements. With respect to teaching or suggesting each and every element of claims 56, 67 and 73, applicants state that the dimerized scFv antibodies of de Kruif-A were derived from a library constructed from multiple light chains, and the libraries of Hoogenboom and Winter (1992) or Nissim (1994) that were mentioned were not the subject of either de Kruif-A or de Kruif-B. This is not found persuasive because, while de Kruif-A contained an example that did not encompass dimerized scFvs where the light chain in each of the scFv comprised the same amino acid sequence, de Kruif-A did provide the general teaching that in a method of making dimerized scFvs for the purpose of making bispecific immunoglobulins one could look to different

examples of antibody libraries. It turns out that at least two of these suggested libraries were ones containing collections of heavy chain variable regions combined with one light chain variable region.

With respect to an articulation of an "obvious to try" rationale, while the examiner did not set forth the arguments in exactly the manner that applicant does in the response, all of the information is provided by the rejection set forth in the previous Office action. Applicants state that the examiner must articulate a finding at the time of the invention that there had been a recognized problem or need in the art which may include a design need or market pressure to solve a problem. The problem or need in the art was how to make bispecific antibodies efficiently. This was recognized by Carter-B in the teaching and suggestion of methods of making bispecific antibodies where formation of a heterodimer is favored over formation of a homodimer. Additionally, Carter-B recognized that two polypeptides making up the heterodimer could comprise scFv antibody fragments (page 10, lines 16-25, and lines 37-46; page 11, lines 17-24; and page 19, lines 2-7; page 21, lines 3-17; pointed to in previous Office action on page 9, lines 5-6). In the use of scFv antibody fragments in making bispecific antibodies, one may have two previously known parent antibodies, and clone out the appropriate regions to make the two scFv antibody fragments and use the light chain from each of the two parent antibodies. Alternatively, as taught by de Kruif-A, one could look to antibody fragment libraries as a source for the two binding sites of a bispecific antibody. At the time of the invention, it appears that there were a finite number of such libraries and at least two of them were Hoogenboom and Winter (1992) library and the Nissim library (1994), which are libraries characterized by de Kruif-B as containing a collection of V_H genes combined with one V_L gene. Furthermore, de

Kruif-A provides a suggestion for using these libraries. Given that de Kruif-A successfully made a bispecific immunoglobulin using scFv antibody fragments, it appears that one of ordinary skill in the art could have pursued the suggestion to make a bispecific antibody using any of the suggested libraries with a reasonable expectation of success. Therefore, it was concluded that it would have been obvious to try to use the methods of Carter-B (which encompassed making bispecific antibodies using scFv antibody fragments) to make dimerized scFv bispecific antibodies having a multimerization domain; and to obtain the scFv sequences from phage libraries as taught and suggested by de Kruif-A, which teaches a successful dimerization of scFvs to make a bispecific immunoglobulin, and to use one of the libraries suggested by de Kruif A, which would necessarily result in a bispecific immunoglobulin where each binding domain had the same light chain if one used the library of Hoogenboom and Winter or of Nissim. Because there appears to have been a finite number of libraries it appears that one could easily have chosen either of these libraries.

Additionally applicants argue that there is no motivation to make a restricted library, that the references teach away from the present invention, and that the examiner used improper hindsight in formulating the rejection. These arguments are not found persuasive because the rejection is not based on the argument that it would have been obvious to make a restricted scFv library. Instead the argument is based on the fact that such libraries already existed at the time filing, and that the prior art contained a suggestion to use such libraries. With respect to improper hindsight, applicants state that the examiner picked and chose selected portions of Carter-B which were then combined with de Kruif-A and de Kruif-B in an attempt to recreate the claimed invention. This is not the case at all. To show which elements of the invention were

provided by Carter-B, the examiner pointed to various positions in the document to show where specific teachings of claim limitations were to be found. The next question to answer was if in practicing a specific embodiment of Carter-B (use of scFv fragments in making a bispecific antibody), there was any further guidance in the prior art. The examiner found such guidance in de Kruif-A and used de Kruif-B to understand the nature of scFv libraries suggested by de Kruif-A. Because de Kruif-A successfully uses an scFv library to make a bispecific antibody and because de Kruif-A points to specific libraries as sources for scFv sequences the examiner concluded it would be obvious to try to make bispecific antibodies of Carter-B with the libraries of de Kruif A, where using at least two of them would necessarily result in structures that are the same as those made by claimed methods.

Claims 56, 57, 67 and 69 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hu (Hu, S.-z., et al., Cancer Research, 56: 3053-3061, 1996) in view of de Kruif-A (supra) and further in view of de Kruif-B (supra) for the reasons of record.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that the examiner cites references that do not teach or suggest all of the elements in the claims, that the examiner fails to articulate an "obvious to try" rationale, that the references teach away from the present invention, and the examiner uses improper hindsight in formulating the rejection. These are arguments that are essentially the same as those presented for the rejection above, and there does not appear to be any discussion of the particular teachings of Hu (as

opposed to Carter-B) for why the rejection should be withdrawn. Therefore, for the reasons set forth above, applicants' arguments are not convincing and the rejections is maintained.

Conclusion

No claim is allowed. Claim 77 is objected to for depending from a rejected claim.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry

Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
October 27, 2008

/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643